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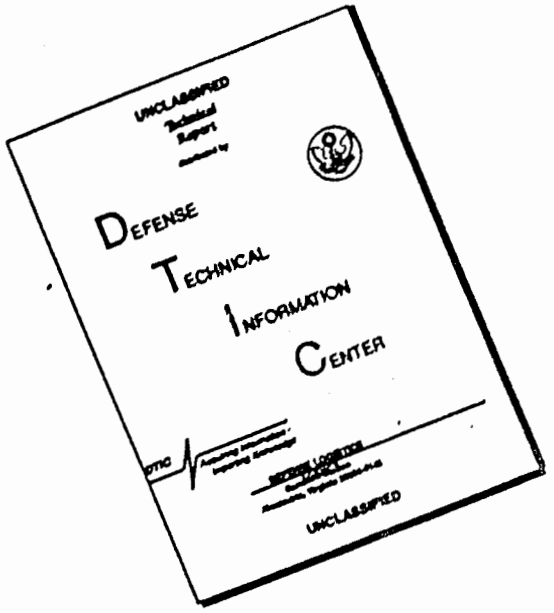

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THE INFLUENCE OF DISEASE IRRITANTS IN AEROSOL FORM ETIOLOGY, EPIDEMIOLOGY, AND LABORATORY DIAGNOSIS OF SOME ACUTE VIRUS DISEASES IN THE RESPIRATORY TRACT

[Following is the translation of an article by Dr. Karl-Heinz Husmann of the Hygiene Institute at the Johannes Gutenberg University in Mainz (Director Professor Dr. H. Kliewe), in Fortschritte der biologischen Aerosol-Forschung (Progress in the Biological Research of Aerosol), 1957-1961, pages 137-147.]

Acute infections of the respiratory tract considerably contribute to the general morbidity rate of a population. In many respects they still are an unsolved problem. Not only clinical and social-hygienic, but also economic aspects are important in the evaluation of this problem. The clinical symptoms of both the sporadically and epidemically acute respiratory tract infections appear in many forms, ranging from the common cold and influenza-like symptoms to primary atypical pneumonia. Only a small percentage is conditioned by bacteria, primarily streptococci. The largest part of these diseases is caused by viruses. The introduction of modern cell culture methods to virological research made it possible during recent years to arrive at an etiological clarification of infections which had often been erroneously described as "colds." Vivell's (55) Table 1 gives a survey of viruses which may be regarded as irritants of respiratory diseases (Table 1). Of this large number of irritants, we intend to concentrate in the adenovirus group, and to discuss it primarily from the points of view of etiology, epidemiology, and laboratory diagnosis.

It is the purpose of this paper to demonstrate an example of the actual problem of virology and to point out several unsolved problems which may be satisfactorily explained only in the light of aerosol research.

In 1953, while studying the growth of adenoids and tonsils which had been removed by operation, Rowe and co-workers (47) succeeded in isolating a cytopathogenic agent. This agent remained intact in other passages of HeLa-cell cultures, and was temporarily called the "adenoid degeneration agent" (abbreviated A. D. - Agens), because at that time the correlation with respiratory infections was not as yet known. Almost at the very same time, in the year 1954, Hilleman and Werner (28) recovered a new virus in the pharyngeal fluid of recruits during the epidemic of a respiratory infection. They called this virus the A.R.D. - virus (=acute respiratory disease virus), or "R.I. - 67 - agent" (i.E. respiratory illness 67). In this case as well, the cultivation in passages of HeLa - cell cultures was successful. The cell

stem, which had originally been obtained from a human carcinoma, has been cultured successfully in vitro since 1951. While the findings of Rowe and co-workers showed a latent infection of the adenoids and tonsils which was discovered through pure coincidence, in the second case the isolated virus was, without doubt, the etiological agent of an acute respiratory illness. This was also demonstrated in experiments where volunteers were infected with it.

The early reports generally enlivened the studies concerned with the etiological clarification of acute respiratory diseases. A few years produced such an abundance of material concerning the adenoviruses and the diseases caused by them that we may indeed point to the output as a model example of virological efforts. At the same time, the intensive research lead to linguistic confusion in that various names were applied to this group of irritants such as R.I.-67 -virus, A.D.-virus, A.R.D.-virus, and A.P.C. (=adenoidal pharyngeal conjunctival)-virus. In order to avoid future difficulties in nomenclature, it was agreed to adopt a uniform term denoting this virus group; namely, adenoviruses (14).

The adenoviruses represent a group of virus types which can be differentiated serologically and have largely common morphological, physical-chemical, and serological properties. They are apathogenic to the remaining laboratory animals, and cannot be cultured in incubated chicken embryos. On the other hand, they possess a clear affinity to the epithelim cells of monkeys and humans, where they produce characteristic cytopathogenic effects. All adenoviruses known so far will multiply in cultures of monkey kidneys and HeLa-cells. In addition, other cell types are used, as for example, human amnio cells and KB cells. The latter stem from the HeLa-cells of human tumor tissue. During the relatively long period of four to six hours, adenoviruses are absorbed at some 75% by HeLa-cells (8, 20, 21, 44). Depending on the type of cells and viruses, the ecliptic phase lasts for 14 to 21 hours (3, 19, 21), (eclipse is the term applied to the latent phase, when the presence of the virus in the main cell is masked and cannot be determined). Within 24 hours following the inoculation, enclosures begin to appear in the core of the HeLa-cell. They may be discerned through color, are roundish, and surrounded by a light zone; at the beginning they are acidophile and Feulgen-negative, later they become basophile and Feulgen-positive. These enclosures become larger, while the rest of the core degenerates for the most part and finally is completely destroyed (8, 56). In contrast to this "late" cytopathogenic effect, which materializes only after a lengthy period of incubation, which is caused by the virus itself, and which is chiefly characterized by the damage done to the core of the cell, the first or early cytopathogenic effect appears through a protein factor which can be detached from the virus (42, 48). This "cell-detachment-factor" (abbreviated C.D.F.), which is smaller and more resistant to heat and UV rays than the infectious virus particle itself, after a short period of time (four to six hours) first causes a roundness and clotting, and finally, within three to five days after the inoculation, leads to a progressive destruction and

Table 1. Viruses as Irritants of Respiratory Tract Illnesses

IRRITANT	GROUP	TYPES	CLINIC
A. Influenza viruses	A	Numerous	Typical influenza
	A 1	Numerous	Typical influenza
	A 2	A/Asia	Typical influenza
	B	2	Typical influenza
	C	--	Typical influenza
B. Parainfluenza virus	1	Sendai	Infant pneumonia
		or HVJ	Pneumonia
		HA Type 2	Influenza infections
		Cop 222	Croup
	2	CA	Croup, laryngeal tracheo-bronchitis
	3	HA Type 1	Pneumonia
		EA 102	Pharyngitis and minor infections of the respiratory tract
	SA virus	--	?
C. Adenoviruses		3,4,5,7,14	ARD in recruits and adults
	8	8	Epidemic kerato-conjunctivitis
		1-9,14-17	Follicular conjunctivitis, often with fever and general infection
		1-7	Abacterial pharyngitis in children
		1-7,9,14	Pharyngeal-conjunctival fever
		4,7	Virus pneumonia without cold, up to lethal results
		1-5,7	Croup, lymphadenitis, encephalitis, menengitis, and exanthema
D. ECHO-viruses		ECHO Type 11 (U-virus)	Croup, light infection of upper respiratory tract
		ECHO Type 20 (JV-1-virus)	Feverish cold Diarrhea
		JH 1 and 2060	Cold, light respiratory infection

Table 1. Viruses as Irritants of Respiratory Tract Illnesses (Cont)

IRRITANT	GROUP	TYPES	CLINIC
E. PAP virus	PAP	--	Primary atypical pneumonia with cold agglutination. Abacterial respiratory infections in varying degrees
F. Other viruses, not specified	Coe	--	Pharyngitis, cold
	CCA and respiratory syncytial virus		Cold in chimpanzees
			Bronchial pneumonia in children
G. Common cold	?	?	Cold
H. Reo-viruses		1	Healthy children
		2	Cold, diarrhea
		3	Diarrhea, light infections

dissolution of cells from the surface of the vascular culture. As the antigen indications show, there is an intranuclear reproduction of the virus; however, it becomes fully infectious only in the cytoplasma. Electron-microscopic tests of an infected HeLa cell show a concentration of viruses like crystalline aggregates in the nucleus (7). The individual virus particle has a diameter of 50-65, or 80-120 mu, depending on the method of measurement used (35, 37, 56). At temperatures of about 4° C, the adenoviruses remain infectious for a long period of time (at least four months). They withstand repeated freezing and defrosting without considerable loss of activity. Changes in the oxygen concentration at pH 3.1 - 9.4 bearly diminish the infectiousness. A characteristic of the adenoviruses is their resistance to ether; that is, a treatment with a 20 % diethylether lasting 18 hours fails to produce a marked change in the infection (22, 38, 46). Formalin concentrated up to 1:4000 inactivates adenoviruses without the loss of antigen (27, 31). Almost like all viruses, they are resistant to sulfonamide and antibiotics.

From the serological point of view, the adenovirus group is characterized by a specific complement-fixing S-antigen which is common to all sub-groups or types. On the other hand, the neutralizing antibodies are type specific, which makes an exact type diagnosis of isolated adenoviruses possible. Currently there are more than 20 adenovirus types known which can be differentiated serologically (45).

In principle, there are the same possibilities in the laboratory diagnosis of adenovirus infections as of other virus types: first of all, the attempt to prove the irritant, and secondly, the serological diagnosis following the detection of antibodies in the patient's serum. For the purpose of isolating and identifying the infected agent, the pharyngeal fluid of the patient is injected into the tissue culture, preferably during the early days of the illness. In addition to primary transplanted cultures, there are others suited for this purpose, such as permanent cells from the human amnio tissue, as well as cell cultures of malignant origin, as for example, the HeLa and Kb-cells (particularly the so-called "monolayers"). Supposedly the virus can be isolated from the faeces a considerable time after the manifestation of the illness. The presence of adenoviruses may be microscopically detected through the appearance of cytopathogenic effects which have already been mentioned. It may be determined through the complement agglutination reaction whether or not the isolated virus belongs to the adenovirus group. The centrifuged and inactivated portion of the tissue culture containing the virus then serves as antigen, while a convalescent serum supplies the antibodies. A special type diagnosis is done with the aid of the virus neutralization test, using monotypical antiserum obtainable from rabbits, following repeated intravenous injections of the live virus.

Both the KBR and neutralization tests are available for the serologic laboratory diagnosis of adenovirus infections. In every serologic diagnosis, a serum pair must be examined in order to determine a possible increase in the antibody titer. The first blood test is done as soon as possible after the outbreak of the illness, the second some two to three weeks later, during the convalescent stage. The criterium of neutralization is the complete stoppage of the cytopathogenic effect in the test cultures as compared to the virus controls. If the antibodies have increased at least four times, this is considered to be proof of a contact with adenoviruses. Unfortunately, the current possibilities in laboratory diagnosis of virus diseases are, generally speaking, insufficient for the clinical physician who is primarily concerned with an etiological clarification. There is a general attempt to improve the methods, and we have particularly good reasons to expect a great deal from fluorescent-serologic methods. The domain of virological laboratory diagnosis is currently still the study of epidemiological interactions.

The epidemiology of adenovirus infections draws the particular interest of aerosol research. Following the observations up-to-date, it may be assumed that adenoviruses are spread throughout the world. Numerous epidemics in different parts of the world were etiologically related to the adenovirus group (2, 5, 6, 10, 13, 16, 17, 18, 29, 33, 41, 49, 51, 53, 54). The most frequent epidemics occur in military establishments among young recruits. Gsell (26), Loffler and co-workers (36), as well as Kaufmann and co-workers (34) report about the epidemic occurrence of adenovirus infections in Switzerland. Glander v. Harnack and Lippelt, Breckhoff, as well as Mumme (9, 23, 39) observed epidemics among adults and children in Germany. In addition, systematic serological studies of healthy people (1, 15, 17, 40, 50) have shown that adenovirus

occur almost ubiquitously. There is no doubt that the fight with the irritants begins in early childhood, when numerous infections surely take a latent or abortive course. Jordan's (32) findings show the degree of infectiousness in childhood. From over 90% of the children's tonsils he studied, he was able to isolate adenoviruses of type 1, 2, and 5. Reports concerning the degree of infectiousness among the population, done by various researchers on the basis of serological data, do not always agree. In any case, the most frequent occurrence of antibodies was found among people between the ages of 18 and 30.

The pathogenetic and epidemiological importance of the individual adenovirus types varies greatly (Table 2). Table 2, drawn up by Vivell (55) with references to Huebner (30), as well as Kaufmann and co-workers (34), shows which adenovirus types should be related to the different clinical syndromes. It also shows that some types (types 3, 4, 7, 8, and 14) usually occur as an epidemic. Type 8 takes an unique position in this respect, because it should be related to the epidemic kerato-conjunctivitis. In addition, the different adenovirus types show a noteworthy predilection for certain groups of the population.

Sex differences do not change the disposition to adenovirus infections. The epidemic seems to be favored by close contact and similar conditions, such as barracks, orphanages, hospitals, and summer camps. Adenoviruses are primarily spread through the air as a crystalline infection. It should be mentioned, however, that an infection method such as in the case of entero-viruses should be possible, since large quantitites of the virus escape with the faeces. The rapid spreading of the virus and its frequency in the upper respiratory tract indicate, however, that the air-borne infection is the most common one. American authors include the crystalline infection in contact infections, since it occurs at very short distance through a spray of secreted crystals containing germs when speaking, coughing, and sneezing. The actual air-borne infection materializes through germs which survive in the air for a lengthy period of time in the form of crystals, or else live in the dust and whirl up into the air. It is difficult to determine without an experiment in how far an air-borne infection is the basis of adenovirus infections. Apart from volunteers in America and in England (11, 43, and others) who were injected with the nasal and pharyngeal secretion of infected persons, or inhaled filtered nasal discharge, there are no experiments to solve the problem of adenovirus infection as a possible air-borne infection. There is also only a limited number of publications dealing with the spreading and infectiousness of human pathogenic viruses in aerosol. Due to their relatively low danger, adenoviruses are model germs for experiment purposes. We have started with testing the survival of artificial adenovirus aerosols. We do not intend to report on these experiments, which are still in the early stages, at this point. An accurate knowledge of this interaction is most desirable, not only from the epidemiological point of view, but also in respect to an efficient expositionary prophylaxis. Since a chemotherapy with virustatic or virucide means does not as yet exist,

Table 2: Pathogenetic Importance of Adenovirus Types

Illnesses	Adenovirus types																
	1	2	3	4	5	6	7a	8	9	10	11	12	13	14	15	16	17
1. ARD in recruits and older people			X	X	+		X							X			
2. Epidemic kerato-conjunctivitis			?				?	X									
3. Follicular conjunctivitis	+	+	X	+	+	+	X	+	+	+	+	+	+	+	+	+	+
4. Abacterial pharyngitis in children	+	+	X	+	+	+	X										
5. Pharyngeal-conjunctival fever	+	+	X	X	+	+	X		+					X			
6. Virus pneumonia without cold agglutinins			X				X										
7. Other symptoms, such as croup, lymphadenitis, mesenterialis, encephalitis, meningitis, and exanthema		+	+	+			+										

X = epidemic occurence
+ = sporadic

prophylactic measures in the prevention of respiratory virus infections are particularly important. An active immunization with vaccines promises success in the case of adenovirus infections (4, 12, 27, 52), unlike in the case of other acute virus infections in the respiratory tract. Bivalent or trivalent vaccines containing the virus types 4 and 7, or 3, 4, and 7, induced a significant increase in the agglutinating and homologous neutralizing antibodies following even one injection of 1 ml vaccine. This vaccine was prepared according to the principle of the Salk vaccine for the prevention of poliomyelitis; that is, it contained a formalin-inactivated virus from old tissue cultures. This vaccine is supposed to have reduced the morbidity rate among American Army recruits by over 90%. The opinions vary pertaining to the practical significance of this preventive vaccine among the civilian population. So far, there have been no reports concerning the influence of disinfection measures on the spreading of adenoviruses. As the exposition increases, the application of UV-rays, chemicals in aerosol form to disinfect the air, and mouth disinfectants will meet with only limited success. Nevertheless, we are of the opinion that in order to prevent an infection of such high morbidity (some 80% of all receptive people get it), all specific and non-specific prophylactic measures available should be utilized, even though the mortality rate of this disease is insignificant. If we consider the fact that the adenoviruses form only a part of the irritants of acute respiratory infections, it becomes clear what difficulties exist in the diagnosis and an effective prophylaxis. The acute respiratory virus infections become even more important when we consider that apart from being a medical-clinical problem, these illnesses represent a considerable social-hygienic and economic problem. Besides presenting a danger at all types of human gatherings, they are the cause of frequent employee absenteeism. It is to be hoped that an intensive cooperation among all interested groups will achieve progress in this important field of research during the coming years.

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